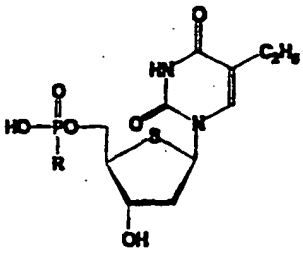


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<p>(21) International Application Number: PCT/CA99/00465 (22) International Filing Date: 1 June 1999 (01.06.99) (30) Priority Data: 60/087,569 1 June 1998 (01.06.98) US (71) Applicant (for all designated States except US): S &amp; T SCIENCE AND TECHNOLOGY INC. [-/-]; P.O. Box 3443, Tropic Isle Building, Road Town, Tortola (VG). (72) Inventors; and (75) Inventors/Applicants (for US only): ALEXANDROVNA, Alexandrova Lioudmila [RU/RU]; ul. Fersmana, 3-70, Moscow, B-312 117312 (RU). ANTONOVICH, Krayevsky Alexander [RU/RU]; Profsovnaya al. 132-4-11, Moscow, 117321 (RU). ADANI, Alexander [CA/CA]; 126 Pine Valley Crescent, Woodbridge, Ontario L4L 2W4 (CA). (74) Agents: NASSIF, Omar, A. et al.; Gowling, Strathy &amp; Henderson, Suite 4900, Commerce Court West, Toronto, Ontario M5L 1J3 (CA).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: ANTIVIRAL PHOSPHORUS DERIVATIVES OF 4'-THIO-5-ETHYL-2'-DEOXYURIDINE</p> <div style="text-align: center;">  <p>(II)</p> </div> <p>(57) Abstract 4'-Thio-5-ethyl-2'-deoxyuridine 5'-phosphonate of formula (II) wherein R=H, CONH<sub>2</sub>, AlkylOOC, Alkyl, Haloidalkyl, di-haloidalkyls, trihaloidalkyl, HOCH<sub>2</sub>, AcylOCH<sub>2</sub>.</p>		

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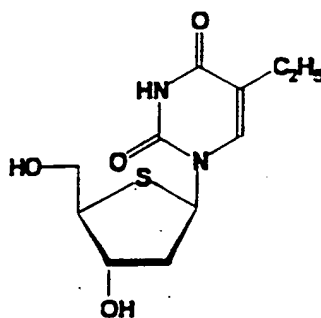
## ANTIVIRAL PHOSPHORUS DERIVATIVES OF 4'-THIO-5-ETHYL-2'-DEOXYURIDINE

## FIELD OF THE INVENTION

The present invention relates to novel inhibitors and, more specifically, to novel 4'-thio-5-ethyl-2'-deoxyuridine 5'-phosphonates, which inhibit the reproduction of the human Herpes viruses (HSV-1, HSV-2, TK<sup>-</sup> HSV-1), Human Cytomegalovirus (HCMV) and Vaccinia virus (VV) in cell cultures.

## BACKGROUND OF THE INVENTION

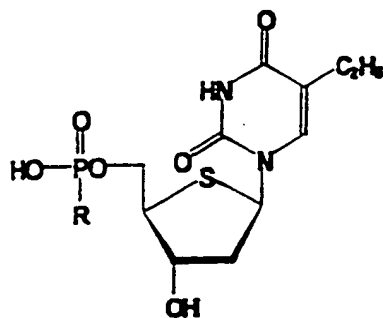
Known in the art are various compounds inhibiting the reproduction of the human Herpes viruses (HSV). The compounds known as TEDU (4'-thio-5-ethyl-2'-deoxyuridine) (Formula I) and as shown below, inhibits HSV (HSV-1, HSV-2) reproduction in cell cultures but it has two negative properties. First, TEDU has generally unacceptable toxicity in human and cell free systems with DNA polymerases. Second, TEDU does not inhibit thymidine kinase defective (TK<sup>-</sup> HSV-1) herpes viruses [1-3].



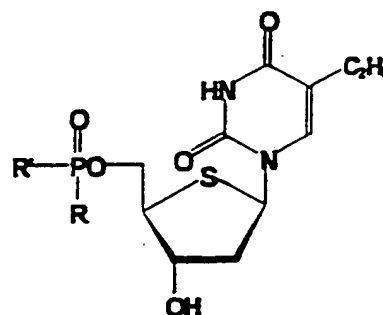
(I)

## SUMMARY OF THE INVENTION

The present invention is directed to novel compounds exhibiting a selective inhibition of the reproduction of the HSV-1, HSV-2, TK<sup>-</sup> HSV, HCMV and VV and which possess low toxicity. The present compounds are II and III of the formula as follows:



(II)



(III)

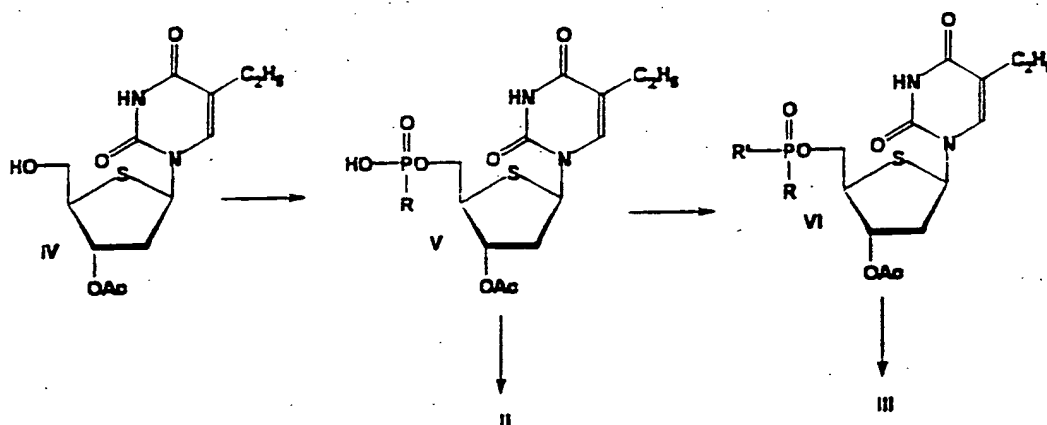
wherein for Formula II, R=H, CONH<sub>2</sub>, AlkylOOC, Alkyl, Haloidalkyl, dihaloidalkyls, trihaloidalkyls, HOCH<sub>2</sub>, AcylOCH<sub>2</sub>, and wherein for Formula III, R= is as defined in Formula II and R'=O-alkyl, O-aminoalkyls, O-hydroxyalkyls, O-glycosyl

These compounds of Formula II and III are capable of inhibiting the reproduction of HSV and are less toxic as compared to the prior art compounds.

**DETAILED DESCRIPTION OF THE INVENTION**

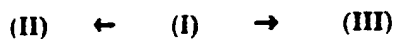
Synthesis of compounds II and III can be made according to Scheme 1 (one arrow essentially corresponds to one chemical step).

Scheme 1



Another synthetic pathway which may be used does not invite the preliminary protection of 3'-hydroxyl as set out in Scheme 2 below (here also one arrow essentially corresponds to one chemical step). According to Scheme 2, synthesis of compounds of Formula II and III are developed with essentially one chemical step starting from the compound of Formula I. Selection between Schemes 1 and 2 generally depends on the yield of the desired compound. In some cases, the yield is higher when the desired compound is synthesized according to Scheme 1, but in another cases Scheme 2 produces higher yields. Yields of II and III ranged from 20-70% with schemes 1 and 2.

Scheme 2



The compounds according to the present invention are white amorphous powders, readily soluble in water, with low solubility in ethanol and dimethylsulfoxide. They have been found generally to be insoluble in other organic solvents.

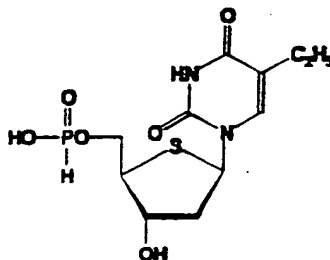
The purity and structure of the compounds according to the present invention were proven by chromatography, UV, mass- and NMR-spectroscopy.

#### EXAMPLE 1

3'-O-Aceryl-I was synthesized according to [3].

Synthesis of 4'-thio-5-ethyl-2'-deoxyuridine 5'-hydrogenphosphonate (II, R=H)

(Scheme 1).



To a solution of phosphite acid (51 mg, 0.8 mmol) in water (2 ml), pyridine (3ml) and tri-*n*-butylamine (148 mg, 0.8 mmol) was added. The solution was evaporated, coevaporated with pyridine (3x5 ml) and then with dimethylformamide (3x5 ml). The residue was dissolved in pyridine (5 ml), 4'-thio-5-ethyl-2'-deoxy-3'-O-aceryluridine (IV, 180 mg, 0.57 mmol) and *N,N*-dicyclohexylcarbodiimide (800 mg, 3.8 mmol) were added. The reaction was mixed at +20°C for 20 h, then ice-cold water (5 ml) was added. After mixing during 1 h at +4°C the reaction was diluted with water (150 ml) and applied onto a DEAE-Toyopearl column (2.5 x 12 cm. HCO<sub>3</sub><sup>-</sup> form), elution was made with a linear gradient of NH<sub>4</sub>HCO<sub>3</sub> (0 -> 0.15M, 1 l). The fractions containing the product

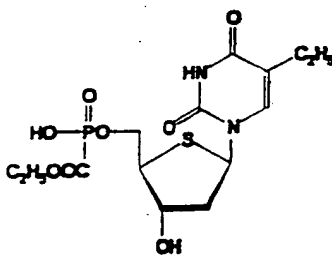
were evaporated and coevaporated with water (3 x 10 ml). The residue was dissolved in 25%  $\text{NH}_4\text{OH}$  and kept at  $+4^\circ\text{C}$  for 20 h. then evaporated. coevaporated with water (2x5ml). Then it was purified on a LiChroprep RP-18 column (2 x 15 cm), elution was made with 0.01M  $\text{NH}_4\text{HCO}_3$  to yield 120 mg (63%).

UV (water)  $\lambda_{\text{max}}$  272nm ( $\epsilon$  9800).  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ ), ppm,  $J$  Hz: 7.77s (1H, H-6), 6.69 d (1H,  $J_{\text{HP}}$  632, H-P), 6.25dd (1H,  $J$  2,  $J$  7.5, H-1'), 4.52m (1H, H-3'), 3.86-4.05m, (2H, 5'a, 5'b), 3.55m (1H, H-4'), 2.17-2.40 m (4H, 2'a, 2'b,  $\text{CH}_2(\text{Ura})$ ), 1.0 t (3H,  $J$  7.5,  $\text{CH}_3\text{CH}_2(\text{Ura})$ ).  $^{31}\text{P-NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  7.2s. Mass:  $m/z$ : 336 [ $\text{M}^+-1$ ].

## EXAMPLE 2

Synthesis of 4'-thio-5-ethyl-2'-deoxyuridine 5'-ethoxycarbonylphosphonate (II,  $\text{R}=\text{COOEt}$ )

(Scheme 2)



To a solution of morpholinium ethoxycarbonylphosphonate (59.3 mg, 0.24 mmol) in water Dowex 50W ( $\text{Py}^+$ , 0.5 ml) was added. The precipitate was filtered, washed with water (10 ml), pyridine (5 ml) and tri-*n*-butylamine (44 mg, 0.24 mmol) was added, the resulting solution was evaporated, coevaporated with pyridine (3x5 ml), dissolved in pyridine and 4'-thio-5-ethyl-2'-deoxyuridine I (54 mg, 0.2 mmol) in was added. The solution was evaporated with pyridine (3x5 ml) and dimethylformamide (3x5 ml). The residue was dissolved in dimethylformamide (5 ml) and then

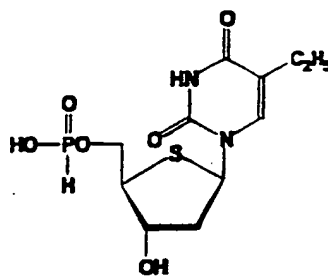
*N,N'*-dicyclohexylcarbodiimide (124 mg, 0.6 mmol) was added, the reaction mixture was kept at +20°C for 20 h, then cold water (5 ml) was added. After mixing for 1 h at +4°C the mixture was diluted with water (150 ml) and applied onto a DEAE-Toyopearl column (2.5 x 12 cm, HCO<sub>3</sub><sup>-</sup>-form), elution was made with a linear gradient of NH<sub>4</sub>HCO<sub>3</sub> (0 → 0.15M, 1 l). The fractions containing the product were evaporated and coevaporated with water (3 x 10 ml). The residue was purified on a LiChroprep RP-8 column (2 x 15 cm), elution being made with a linear gradient of MeOH (0 → 10%, 1 l) in 0.01M NH<sub>4</sub>HCO<sub>3</sub> to yield 35 mg (43%).

UV (water)  $\lambda_{\max}$  272nm ( $\epsilon$  9800), <sup>1</sup>H-NMR (D<sub>2</sub>O),  $\delta$ , ppm, *J* Hz: 7.77s (1H, H-6), 6.25dd (1H, *J* 2, *J* 7.5, H-1'), 4.65m (1H, H-3'), 3.9-4.1m (3H, CH<sub>3</sub>CH<sub>2</sub>O, 5'a, 5'b), 3.55m (1H, H-4'), 2.37-2.40 m (1H, 2'a), 2.21-2.28 m (3H, 2'b, CH<sub>2</sub>(Ura)), 1.18 dt (3H, *J*<sub>CH<sub>2</sub>P</sub> 1.1, *J*<sub>CH<sub>2</sub>CH<sub>2</sub></sub> 7, CH<sub>3</sub>CH<sub>2</sub>O), 0.98t (3H, *J* 7.5, CH<sub>3</sub>CH<sub>2</sub> (Ura)). <sup>31</sup>P-NMR (D<sub>2</sub>O)  $\delta$  -3.9s. Mass: *m/z*: 408 [M<sup>+</sup>].

### EXAMPLE 3

Synthesis of 4'-thio-5-ethyl-2'-deoxyuridine 5'-hydrogenphosphonate (II, R=H)

(Scheme 2)



To a solution of phosphite acid (51 mg, 0.8 mmol) in water (2 ml) pyridine (3 ml) and tri-*n*-butylamine (148 mg, 0.8 mmol) was added. The solution was evaporated, coevaporated with pyridine (3x5 ml) and then with dimethylformamide (3x5 ml). The residue was dissolved in pyridine (5 ml), 4'-

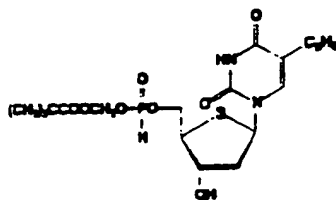


thio-5-ethyl-2'-deoxyuridine (1, 165 mg, 0.57 mmol) and *N,N'*-dicyclohexylcarbodiimide (800 mg, 3.8 mmol) were added. The reaction was mixed at +20°C for 20 h, then ice-cold water (5 ml) was added. After mixing during 1 h at +4°C the reaction was diluted with water (150 ml) and applied onto a DEAE-Toyoparl column (2.5 x 12 cm, HCO<sub>3</sub><sup>-</sup> form), elution was made with a linear gradient of NH<sub>4</sub>HCO<sub>3</sub> (0 - > 0.15M, 1 l). The fractions containing the product were evaporated and coevaporated with water (3 x 10 ml). The residue was purified on a LiChroprep RP-18 column (2 x 15 cm), elution was made with 0.01M NH<sub>4</sub>HCO<sub>3</sub> to yield 90 mg (47%).

UV (water)  $\lambda_{\max}$  272nm ( $\epsilon$  9800). <sup>1</sup>H-NMR (D<sub>2</sub>O), ppm,  $J$  Hz: 7.77s (1H, H-6), 6.69 d (1H,  $J_{\text{H-P}}$  632, H-P), 6.25dd (1H,  $J$  2,  $J$  7.5, H-1'), 4.52m (1H, H-3'), 3.86-4.05m, (2H, 5'a, 5'b), 3.55m (1H, H-4'), 2.17-2.40 m (4H, 2'a, 2'b, CH<sub>2</sub>(Ura)), 1.0 t (3H,  $J$  7.5, CH<sub>3</sub>CH<sub>2</sub> (Ura)). <sup>31</sup>P-NMR (D<sub>2</sub>O)  $\delta$  7.2s. Mass:  $m/z$  336 [ $M^+$ +1].

#### EXAMPLE 4

Synthesis of 4'-thio-5-ethyl-2'-deoxyuridine 5'-(trimethylcarboxymethylene-hydrogenphosphonate) (III, R=H)



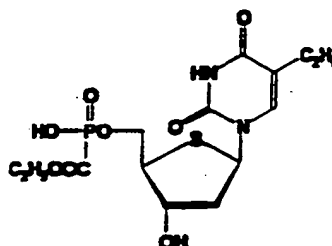
To a solution of trimethylcarboxymethylene hydrogenphosphonate (84 mg, 0.5 mmol) in pyridine (5 ml) tri-*n*-butylamine (93 mg, 0.5 mmol) was added, the resulting solution was evaporated.

coevaporated with pyridine (3x5 ml), dissolved in pyridine and 4'-thio-5-ethyl-2'-deoxyuridine I (108 mg, 0.4 mmol) in was added. The solution was evaporated with pyridine (3x5 ml) and dimethylformamide (3x5 ml). The residue was dissolved in dimethylformamide (5 ml) and then *N,N'*-dicyclohexylcarbodiimide (248 mg, 1.2 mmol) was added, the reaction mixture was kept at +20°C for 20 h, then cold water (5 ml) was added. After mixing for 1 h at +4°C the mixture was diluted with water (150 ml) and applied onto a DEAE-Toyopearl column (2.5 x 12 cm, HCO<sub>3</sub><sup>-</sup>-form), elution was made with a linear gradient of NH<sub>4</sub>HCO<sub>3</sub> (0 → 0.15M, 1 l). The fractions containing the product were evaporated and coevaporated with water (3 x 10 ml). The residue was purified on a LiChroprep RP-8 column (2 x 15 cm), elution being made with a linear gradient of MeOH (0 → 10%, 1 l) in 0.01M NH<sub>4</sub>HCO<sub>3</sub> to yield 82.5 mg (49%).

UV (water)  $\lambda_{\max}$  272nm ( $\epsilon$  9800), <sup>1</sup>H-NMR (D<sub>2</sub>O),  $\delta$ , ppm, *J*Hz: 7.77s (1H, H-6), 6.69 d (1H, *J*<sub>HP</sub> 632, H-P), 6.22dd (1H, *J* 2, *J* 7.5, H-1'), 5.63d (2H, *J* 14, OCH<sub>2</sub>O), 4.55m (1H, H-3'), 3.8-4.1m (2H, H-5'a, 5'b), 3.52m (1H, H-4'), 2.37-2.40 m (1H, H-2'a), 2.21-2.28 m (3H, 2'b, CH<sub>2</sub>(Ura)), 1.18 s (9H, C(CH<sub>3</sub>)), 0.99t (3H, *J* 7.5, CH<sub>2</sub>CH<sub>2</sub> (Ura)). Mass: *m/z*: 421 [M<sup>+</sup>].

### EXAMPLE 5

#### Viral Plaque Reduction Assays.

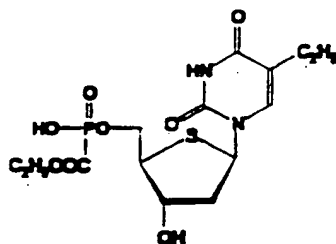


Antiviral assays of II. R=C<sub>2</sub>H<sub>5</sub>OOC were performed using an adaptation of the plaque reduction assay described in [4]. Twenty-four well plates containing monolayers of MCR 5 cells (human embryo lung fibroblasts, ATCC CCL 171) were used for assay of varicella zoster virus (VZV strain G31), and

monolayers of Vero cells (African Green monkey kidney, ATCC CCLB1) were used for herpes simplex virus type 1 (HSV-1) strain SC16 and HSV-2 (strain 186). Monolayers were infected with virus at a multiplicity calculated to produce 60-80 plaques per well. Infected cells were overlaid with liquid growth medium containing various known concentrations of the compound under investigation, and, in the case HSV-1 and HSV-2, carboxymethyl cellulose to prevent the formation of secondary plaques. Following a suitable period of incubation, plaques were fixed with formol saline and stained, and their numbers were determined. For  $IC_{50}$  determination, a dose-response curve was obtained and from this the 50% inhibitory concentration ( $IC_{50}$ ) was obtained. Tables 1 (first testing) and 2 (second independent testing) demonstrate these data for different viruses. The well known antiviral drugs are shown as controls: BVDU - 5-bromovinyl-2'-deoxyuridine; ribovirin; ACG - acyclovir; DHPG - gancyclovir.

#### EXAMPLE 6

Cytotoxicity assay of II,  $R=C_2H_5OOC$



Subconfluent cultures of Vero or MRC-5 cells were grown in 96-well microtiter plates in the presence of different dilutions of drug. Cell numbers present at 96h (Vero) and 7 days (MRC-5) were estimated, on replicate cultures, using uptake of a tetrazolium dye (MTT). The concentration required for a 50% inhibition of cell growth compared to control cell growth in the absence of compound is termed  $CCID_{50}$ . Cytotoxicity assays were performed using Vero cells and MRC-5 cells.

For 50% cytotoxic concentration ( $CC_{50}$ ) determination, a dose-response curve was obtained. Tables 1 (first testing) and 2 (second independent testing) demonstrate these data for cells. The well known antiviral drugs are shown as controls: BVDU - 5-bromovinyl-2'-deoxyuridine; ribovirin; ACG - acyclovir; DHPG - gancyclovir.

The compounds according to the present invention, viz 4'-thio-5-ethyl-2'-deoxyuridine 5'-phosphonates have shown to be capable of selective inhibition of the reproduction of the HSV-1 and HSV-2 viruses in cell cultures. It is expected that this same selective inhibition of the reproduction of TK<sup>+</sup> HSV-1, HSMV and VV viruses will be exhibited by the compounds of Formula II and III. It is expected that the compounds of Formula II and III will be effective in the treatment of these viruses, including prophylactic treatment.

Table I. Antiviral activity and cytotoxicity of TEDU (I) and its phosphonate (II, R=COOEt) in E<sub>6</sub>SM cell cultures.

Compound	minimum cytotoxic concentra- tion, mM	Minimum inhibitory concentration <sup>a</sup> , mM									
		HSV-1 (KOS)	HSV-1 (F)	HSV-1 (Mclaryre)	HSV-2 (O)	HSV-2 (196)	HSV-2 (Lyons)	Vaccine virus	Vesicular stomatitis virus	HSV-1 TK <sup>c</sup> (B2006)	HSV-1 TK <sup>c</sup> (VMAW 1837)
I (I)	>500	0.17-0.5 >(1000- 2950) <sup>c</sup>			2-5 >(100- 250)			0.99 >505			
II, R=CO <sub>2</sub> Et	>950	0.036 >26400	0.036 >26400	0.036 >26400	0.17 >5590	0.17 >5590	0.17 >5590	0.17 >5590	1.45 >660	0.17 >5590	0.17 >5590
BV011	>240	0.046 >5220	0.046 >5220	0.046 >5220	>240	>240	>240	5.76 >42	>1200	48 >5	240
Ribavirin	>1640	1000 >1.6	1000 >1.6	1000 >1.6	1000 >1.6	>1650	1650	200 >8	1000 >1.6	200 >8	200 >8
ACG	355	0.75 430	0.75 430	0.75 430	1.7 210	0.75 430	1.7 210	>355	355	42.6 8.3	8.5 42
D117G	>400	0.15 2670	0.15 2670	0.0045 88900	0.074 5200	0.074 5200	0.074 5200	>400	>400	0.38 1050	0.38 1050

<sup>a</sup> Required to cause a microscopically detectable alteration of normal cell morphology.

<sup>b</sup> Required to reduce virus-induced cytopathogenicity by 50%.

<sup>c</sup> Selectivity Index

Table 2. Antiviral activity and cytotoxicity of TEDU phosphonate (II, R=COOEt) in E<sub>6</sub>BM cell cultures.

Compound	minimum cytotoxic concentra- tion <sup>a</sup> , mM	Minimum inhibitory concentration <sup>b</sup> , mM									
		HSV-1 (KOS)	HSV-1 (F)	HSV-1 (Melanore)	HSV-2 (G)	HSV-2 (196)	HSV-2 (Lysen)	Vesicular virus	Vesicular virus	HSV-1 TK <sup>c</sup> (B2006)	HSV-1 TK <sup>c</sup> (VAMW 1077)
Et <sub>3</sub> R- COOEt	>950	0.036 >26400	0.012 >73200	0.036 >26400	0.17 >5590	0.03 >31700	0.15 >6350		0.30 >3170	7.53 >130	1.5 >635
BVDU	>240	0.077 >3120	0.046 >5220	0.046 >5220	>240	>240	>240		5.76 >42	240	240
Ribavirin	>1640	65.8 >25	65.8 >25	39.5 >40	200 >8	200 >8	200 >8		65.8 >25	65.8 >25	200 >6
ACV	355	0.33 1075	0.115 3085	0.57 625	0.33 1075	0.57 625			>355	14.2 25	8.53 42
DHPG	400	0.015 26700	0.0078 51280	0.005 80000	0.078 5130	0.078 5130	0.125 3200		>400	0.63 635	0.125 3200

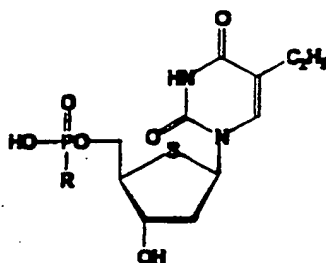
<sup>a</sup> Required to cause a microscopically detectable alteration of normal cell morphology.<sup>b</sup> Required to reduce virus-induced cytopathogenicity by 50%.<sup>c</sup> Selectivity index

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We claim:

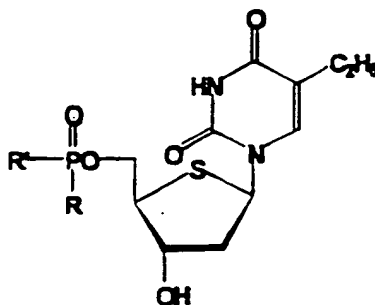
1. 4'-Thio-5-ethyl-2'-deoxyuridine 5'-phosphonate of the formula:



(II)

wherein R=H, CONH<sub>2</sub>, AlkylOOC, Alkyl, Haloidalkyl, dihaloidalkyls, trihaloidalkyl, HOCH<sub>2</sub>, AcylOCH<sub>2</sub>

2. 4'-Thio-5-ethyl-2'-deoxyuridine 5'-phosphonate of the formula (II) of claim 1 for use in selectively inhibiting HSV-1/HSV-2, TK/HSV-1, HCMV and VV:
3. 4'-Thio-5-ethyl-2'-deoxyuridine 5'-phosphonate of the formula (II) of claim 1 for use in the prophylactic treatment of HSV-1, HSV-2, TK/HSV-1, HCMV and VV.
4. 4'-Thio-5-ethyl-2'-deoxyuridine P-substituted 5'-phosphonates of the formula:



(III)



wherein R=H, CONH<sub>2</sub>, AlkylOOC, Alkyl, Haloidalkyl, dihaloidalkyls, trihaloidalkyl, HOCH<sub>2</sub>, AcylOCH<sub>2</sub> and R'=O-alkyl, O-aminoalkyls, O-hydroxyalkyls, O-glycosyl

5. 4'-Thio-5-ethyl-2'-deoxyuridine P-substituted 5'-phosphonates of the formula (III) for use in selectively inhibiting HSV-1, HSV-2, TKHSV-1, HCMV and VV.

6. 4'-Thio-5-ethyl-2'-deoxyuridine P-substituted 5'-phosphonates of the formula (III) for use in the prophylactic treatment of HSV-1, HSV-2, TKHSV-1, HCMV and VV.

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07H19/10 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ALEXANDROVA L A ET AL: "4'-thio-5-ethyl-2'-deoxyuridine 5'-triphosphate (TEDUTP): synthesis and substrate properties in DNA-synthesizing systems" ANTIVIRAL CHEM. CHEMOTHER. (ACCHEH,09563202);1996; VOL.7 (5); PP.237-242, XP002116568 Russian Acad. Sci.;Engelhardt Inst. Molecular Biol.; Moscow; 117984; Russia (RU) cited in the application the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

4 November 1999

Date of mailing of the international search report

17/11/1999

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International Application No

PCT/CA 99/00465

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